REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Office Action mailed on June 2, 2009. Claims 1, 6, and 12-37 had been pending and claims 1 and 6 were examined. Claims 12-37 were withdrawn. Claims 2-5 and 7-11 were previously cancelled without prejudice or disclaimer. Pending entry of this amendment, claim 1 has been amended. Thus, with this amendment, claims 1 and 6 are under consideration.

Claim 1 has been amended to recite "lysing the cell to obtain a cell lysate containing the protein or salt thereof." The amendment finds support in the specification, for example, at least at page 77, lines 1-9, which describes adding lysis solution to cells that carry an Egr-1 expression vector or a control vector. Accordingly, the amendment is fully supported by the specification as filed. Upon entry of the present amendment, claims 1 and 6 will be under consideration.

Rejection of claims 1 and 6 under 35 U.S.C. § 103(a)

Claims 1 and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rupprecht et al. (1997) *Kidney Int.* 51: 694-702 ("Rupprecht") in view of Einstein (WO 01/04356) ("Einstein"), Khachigian (WO 01/30394) ("Khachigian"), McKay et al. (1998) *Anal. Biochem.* 256: 28-34 ("McKay") and Erlich et al. (1997) *Am. J. Pathol.* 150: 873-880 ("Erlich").

The Office alleges that Rupprecht teaches that "Egr-1 induction not only occurs after mitogenic stimulation of mesangial cells (MCs) in culture, but can also be observed with MC proliferation *in vivo* in a rat model of mesangioproliferative glomerulonephritis." Office Action at page 3. The Office further alleges that Rupprecht "tested the effect of various anti-sense oligonucleotides directed against Egr-1 by comprising comparing the expression of Egr-1 at both mRNA and protein levels in rat glomerular mesangial cells stimulated with PDGF in the

presence or absence of antisense oligonucleotides and . . . found that suppression of Egr-1 mRNA and protein induction interfered with MC mitogenesis." *Id.* at pages 3-4. The Office recognizes that Rupprecht "do[es] not teach specifically a method of screening for a therapeutic substance for a renal disease, including diabetic nephropathy (claim 6), wherein said method comprises steps (a)-(g) as recited in independent claim 1." *Id.* at page 4.

The Office contends that Einstein teaches "a screening method for identifying modulators (both inhibitors and/or inducers) of Egr-1 (including human Egr-1) induction." *Id.* According to the Office, the screening method of Einstein includes contacting cells with agents, and "the proteins from 'agent contacted' cells and control, non-agent contacted cells would be compared for changes in the expression and/or activity of Egr-1 such as the ability of Egr-1 to bind to a GSG consensus containing nucleic acid molecule." *Id.* at pages 4-5.

Regarding Khachigian, this document allegedly teaches "a screening method for agents that decrease[] expression, nuclear accumulation and/or activity of Egr-1, including human Egr-1." *Id.* at page 5. The Office also states that Khachigian teaches that "Egr-1 binds to the promoters of a spectrum of genes including tissue factor and PDGF-B." *Id.*

The Office, however, acknowledges that Einstein and Khachigian do not teach "the steps of immobilizing on a solid phase a polynucleotide to which the protein or salt thereof comprising the amino acid sequence of SEQ ID NO:2 (human Egr-1) is capable of binding to and selecting the compound that decreases the level of at least tissue factor." *Id.*

Attempting to remedy that defect, the Office alleges that McKay "teaches an enzyme-linked immunosorbent assay for the detection of agents which interfere with the DNA binding activities of transcription factors exemplified by NF-IL6, wherein the assay involve[s] immobilizing of a target DNA to a solid support and contacting that solid support with a DNA

binding transcription factor protein and an antibody that binds specifically to the DNA binding protein." *Id.* The Office further contends that "this assay quantifies both the expression and binding activity of DNA binding transcription factor proteins." *Id.* at page 6.

According to the Office, Erlich teaches that "increased glomerular tissue factor (TF) expression is assiociated with glomerular fibrin deposition and renal failure in human and experimental crescentic glomerulonephritis, and demonstrated that TF is the major in vivo initiator of fibrin deposition in crescentic glomerulonephritis." *Id.*

Based on the above, the Office concludes that one of skill in the art would be motivated to modify Rupprecht to establish a screening method that "comprises the steps of immobilizing on a solid phase a polynucleotide to which the protein or salt thereof is capable of binding to and selecting the compound that decreases at least tissue factor." *Id.* The Office urges that one of skill in the art would be motivated for three reasons. According to the Office: (1) "screening methods for identifying inhibitors of Egr-1 expression and/or activity have been successfully taught by both Einstein . . . and Khachigian . . . for treating coronary artery disease and cancer, respectively," *id.* at pages 6-7; (2) "the enzyme-lin[k]ed immunosorbent assay of McKay . . . would be desirable and selected by an ordinary skilled artisan because it is readily adapted for robotic manipulation and ideal for high through put screening," *id.* at page 7; and (3) one of skill in the art "would select for an agent that decreases the level of tissue factor since Erlich . . . already taught at least that increased glomerular tissue factor (TF) expression is associated with glomerular fibrin deposition and renal failure in human and experimental crescentic glomerulonephritis," *id.*

Applicants respectfully traverse. Solely to facilitate prosecution, and not in acquiescence to the Office's rejection, claim 1 has been amended to recite "lysing the cell to obtain a cell

lysate containing the protein or salt thereof." McKay does not teach such a step. Instead, McKay adds purified protein to the ELISA. McKay at page 29.

Contrary to the Office's characterization o f McKay, McKay does not teach or suggest "measuring production of the protein or salt thereof and the binding activity of the protein or salt thereof to the polynucleotide" in a single assay. Rather, McKay measures protein production and binding activity in separate assays. First, McKay expressed MBP-NF-IL6 fusion protein in *E. coli*, purified the protein, and resuspended it in amylase buffer. McKay at page 29. Later, McKay adds 33 ng/μl of the fusion protein to the ELISA assay, confirming that McKay had previously quantitated the amount of protein produced by the *E. coli* before adding it to the ELISA assay. Accordingly, McKay does not teach or suggest "measuring production of the protein or salt thereof and the binding activity of the protein or salt thereof to the polynucleotide" in a single assay.

This defect is not remedied by Rupprecht, Einstein, Khachigian, and Erlich, alone or in combination. As acknowledged by the Office, Rupprecht "do[es] not teach specifically a method of screening for a therapeutic substance for a renal disease, including diabetic nephropathy (claim 6), wherein said method comprises steps (a)-(g) as recited in independent claim 1." Office Action at page 4. For example, using Western blotting, Rupprecht measures Egr-1 protein expression after exposure of MC exposure to antisense oligonucleotides. Rupprecht at page 700. Rupprecht does not, however, measure the binding activity of Egr-1 in that same assay.

Einstein discusses assaying "the ability of the protein to bind a substrate such as a GSG consensus comprising nucleic acid or by transactivation of an appropriate gene product," Einstein at page 17, lines 11-12, *see also* page 11, line 21 - page 12, line 14, but does not discuss

assaying the production of the protein in the same assay. Einstein teaches, for example, measuring Erg-1 expression "in a physiologically relevant manner," such as assaying tissues "under conditions which model physiological cardiac cell stimuli." Einstein at page 9, lines 17-19; *see also*, page 9, line 19 - page 11, line 18.

Khachigian describes testing the ability of an agent to decrease the "production of EGR mRNA (by, for example, Northern blot analysis) or EGR protein (by, for example, immunohistochemical analysis or Western blot analysis)." Khachigian at page 15, lines 24-28. Khachigian also describes an assay using a reporter assay to determine whether glucose affected Egr-1 binding activity in vascular endothelial cells. *Id.* at page 26, line 35 - page 27, line 16. Thus, Khachigian teaches measuring protein production and biding activity in separate assays.

Erlich administers anti-tissue factor (TF) antibodies to rabbits and concludes that TF is an initiator of fibrin deposition in crescentic glomerulonephritis. Erlich at page 873. Erlich is silent regarding Egr-1, and therefore, Erlich does not teach or suggest "measuring production of the protein or salt thereof and the binding activity of the protein or salt thereof to the polynucleotide" in a single assay.

In sum, it would not have been obvious to combine the teachings of Rupprecht, Einstein, Khachigian, McKay, and Erlich to develop a single assay comprising "measuring production of the protein or salt thereof and the binding activity of the protein or salt thereof to the polynucleotide" as recited in the present claims. The combination of these references would not have rendered obvious claims 1 and 6, and accordingly, Applications respectfully request withdrawal of the rejection.

Please grant any further extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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